AMENDED CLAIMS
[received by the International Bureau on 10 December 1999 (10.12.99); original claims 1, 6, 11, 12, 18, 25, 30, 53, 54 and 59 amended; remaining claims unchanged (12 pages)]

1. A formulation comprising a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, with a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

2. A formulation of Claim 1, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

3. A formulation of Claim 2, wherein the concentration of FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

4. A formulation of Claim 3, further comprising an isotonicity agent.

5. A formulation of Claim 4, further comprising a physiologically acceptable buffer.

6. A formulation comprising a non-gaseous preparation of FSH or a FSH variant lyophilized in a first vial, and a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

7. A formulation of Claim 1, wherein said FSH or a FSH variant and preservative are in solution.

8. A formulation of Claim 1, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit:(SEQ ID NO:1)

FPDGEFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYYHKS
β-subunit:(SEQ ID NO:2)
RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE
(b):α-subunit:(SEQ ID NO:3)
FPDGEFTTQDCPECKLRENKYFFKLGVPIYQCKGCCFSRAYPTPARSRKTMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI
β-subunit:(SEQ ID NO:4)
NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATACHCGKCNSDSTDCTVRGLGPSYCSFGDMKE
(c):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:6)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE
(d):α-subunit:(SEQ ID NO:7)
FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYYHKS
β-subunit:(SEQ ID NO:8)
NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE
(e):α-subunit:(SEQ ID NO:9)
FPDGEFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYYHKS
β-subunit:(SEQ ID NO:10)
RSCELTNITITVEKEECSFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIRE
(f):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:11)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

(g):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:12)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM
(h):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:13)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

9. A method of treating infertility which comprises administering to a patient in need thereof a formulation according to Claim 1.

10. A method of Claim 9, wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

11. A process for preparing a preserved solution formulation of a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, which comprises admixing said FSH or a FSH variant and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof, in an aqueous diluent.

12. An article of manufacture for human pharmaceutical use, comprising packaging material and a vial comprising a solution of a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, and a preservative solution, wherein said packaging material

comprises a label which indicates that said solution may be held over a period of 24 hours or greater.

13. The article of manufacture of Claim 12, wherein said vial is a glass container having a stopper for multi-use administration.

14. The article of manufacture of Claim 12, wherein said vial is a blister pack, capable of being punctured and used in pulmonary administration.

15. The article of manufacture of Claim 12, wherein said vial is a pen-injector device.

16. An article of manufacture, comprising packaging material, a first vial comprising lyophilized FSH or a FSH variant, containing an alpha and beta subunit, and a second vial comprising a preservative solution, wherein said packaging material comprises a label which instructs a patient to reconstitute the said lyophilized FSH or a FSH variant in the preservative solution for use over a period of of 24 hours or greater.

17. The article of manufacture of Claim 16, wherein said first vial and said second vial are embodied in a pen-injector device.

18. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a preserved solution of a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, said solution being suitable for administration over a period of 24 hours or greater.

19. A method of using a stable solution of FSH or a FSH variant, containing an alpha and beta subunit to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of FSH or a FSH variant in a stable solution, said solution being suitable for administration over a period of 24 hours or greater.

20. The use of at least one alpha or beta polypeptide of a FSH or a FSH variant in the preparation of

a preserved formulation adapted for administration over a period of 24 hours or greater.

21. A stable formulation comprising at least one FSH or a FSH variant, containing an alpha and beta subunit, and phosphate buffer containing saline or a salt, wherein said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

22. A formulation of Claim 21, wherein the concentration of said FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

23. A formulation of Claim 21, further comprising an isotonicity agent.

24. A formulation of Claim 21, wherein said buffer is phosphate buffered saline.

25. A formulation comprising a first vial containing a nongaseous preparation of FSH or a FSH variant containing an alpha and beta subunit, and a second vial containing phosphate buffer containing saline or a salt.

26. A formulation of Claim 21, wherein said FSH or a FSH variant and said phosphate buffer are in solution.

27. A formulation of Claim 21, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit:(SEQ ID NO:1)
FPDGEFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYYHKS
β-subunit:(SEQ ID NO:2)
RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b):α-subunit:(SEQ ID NO:3)
FPDGEFTTQDCPECKLRENKYFFKLGVPIYQCKGCCFSRAYPTPARSRKTMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI
β-subunit:(SEQ ID NO:4)
NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATACHCGKCNSDSTDCTVRGLGPSYCSFGDMKE

(c):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:6)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

(d):α-subunit:(SEQ ID NO:7)
FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYYHKS
β-subunit:(SEQ ID NO:8)
NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e):α-subunit:(SEQ ID NO:9)
FPDGEFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYYHKS
β-subunit:(SEQ ID NO:10)
RSCELTNITITVEKEECSFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKE
LVYETVKVPGCAHHADSLYTYPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIR
E

(f):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:11)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

(g):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:12)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

28. A method of treating infertility which comprises administering to a patient in need thereof a formulation according to Claim 21.

29. A method of Claim,28, wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

30. A process for preparing a stable solution formulation of FSH or a FSH variant, containing an alpha and beta subunit, which comprises admixing a non-gaseous preparation of FSH or a FSH variant with a phosphate buffer containing saline or a salt.

31. An article of manufacture for pharmaceutical use, comprising packaging material and a vial comprising a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, in an aqueous diluent, wherein said packaging material comprises a label which indicates that such solution is suitable for use over a period of 24 hours or greater.

32. The article of manufacture of Claim 31, wherein said vial is a glass container having a stopper for multi-use administration.

33. The article of manufacture of Claim 31, wherein said vial is a blister pack, capable of being punctured and used in pulmonary administration.

34. The article of manufacture of Claim 31, wherein said vial is a pen-injector device.

35. An article of manufacture, comprising packaging material, a first vial comprising a lyophilized FSH or a FSH variant containing, an alpha and beta subunit, and a second vial comprising a stable aqueous diluent, wherein said packaging material comprises a label which instructs a patient to reconstitute said FSH or a FSH

variant in the aqueous diluent to form a solution that is suitable for use over a period of 24 hours or greater.

36. The article of manufacture of Claim 35, wherein said first vial and said second vial are embodied in a pen-injector device.

37. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, in an aqueous phosphate buffered diluent, said solution being suitable for administration over a period of 24 hours or greater.

38. A method of using a solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant in an aqueous diluent suitable for use over a period of 24 hours or greater.

39. The use of at least one polypeptide of a FSH or a FSH variant in the preparation of a stable formulation adapted for administration over a period of 24 hours or greater.

40. A formulation as described herein.

41. An article of manufacture as described herein

42. A process as described herein.

43. A use as described herein.

44. A method as described herein.

45. Use of a formulation of claim 1 for treating infertility in a patient in need thereof.

46. Use of a formulation of claim 1 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

47. Use of a preserved solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, said solution being suitable for administration over a period of 24 hours or greater.

48. Use of a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of said FSH or a FSH variant in a phosphate buffer, containing saline or a salt, over a period of 24 hours or greater.

49. Use of a formulation of Claim 21 for treating infertility in a patient in need thereof.

50. A use of Claim 49 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

51. Use of stable stable solution of purified FSH or a FSH variant, containing an alpha and beta subunit, in a phosphate buffer containing saline or a salt suitable for administration over a period of 24 hours or greater for treating infertility in a patient in need thereof.

52. Use of a stable solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, wherein said stable solution of said FSH or a FSH variant in phosphate buffer containing saline or a salt is suitable for use over a period of 24 hours or greater.

53. A process of producing a formulation comprising admixing a non-gasesous preparation of FSH or a FSH variant, containing an alpha and beta subunit, and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

54. A process of producing a stable formulation comprising admixing at least a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, and a phosphate buffer containing saline or a salt, wherein

said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

55. A process of Claim 53, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

56. A process according to any of Claims 53-54, wherein the concentration of FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

57. A process according to any of Claims 53-54, further admixing an isotonicity agent.

58. A process of Claim 53-54, further admixing a physiologically acceptable buffer.

59. A process comprising preparing a a non-gasesous preparation FSH or a FSH variant lyophilized in a first vial, and preparing a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

60. A process of Claim 59, wherein said FSH or a FSH variant and preservative are further put into solution.

61. A process according to any of claims 53-54, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit:(SEQ ID NO:1)
FPDGEFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYYHKS
β-subunit:(SEQ ID NO:2)
RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b):α-subunit:(SEQ ID NO:3)
FPDGEFTTQDCPECKLRENKYFFKLGVPIYQCKGCCFSRAYPTPARSRKTMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β-subunit:(SEQ ID NO:4)
NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATACHCGKCNSDSTDCTVRGLGPSYCSFGDMKE

(c):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit:(SEQ ID NO:6)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

(d):α-subunit:(SEQ ID NO:7)
FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYYHKS

β-subunit:(SEQ ID NO:8)
NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e):α-subunit:(SEQ ID NO:9)
FPDGEFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYYHKS

β-subunit:(SEQ ID NO:10)
RSCELTNITITVEKEECSFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIRE

(f):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit:(SEQ ID NO:11)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

(g):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit:(SEQ ID NO:12)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h):α-subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit: (SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

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